The PDZ/coiled-coil domain containing protein PIST modulates insulin secretion in MIN6 insulinoma cells by interacting with somatostatin receptor subtype 5

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Abstract The multi-domain protein PIST (protein interacting specifically with Tc10) interacts with the SSTR5 (somatostatin receptor 5) and is responsible for its intracellular localization. Here, we show that PIST is expressed in pancreatic β-cells and interacts with SSTR5 in these cells. PIST expression in MIN6 insulinoma cells is reduced by somatostatin (SST). After stimulation with SST, SSTR5 undergoes internalization together with PIST. MIN6 cells over-expressing PIST display enhanced glucose-stimulated insulin secretion and a decreased sensitivity to SST-induced inhibition of insulin secretion. These data suggest that PIST plays an important role in insulin secretion by regulating SSTR5 availability at the plasma membrane.

Keywords: Somatostatin subtype 5 receptor; PIST; Insulin secretion; Islets

1. Introduction

Somatostatin (SST) is a peptide hormone with a wide spectrum of biological actions. The isoforms, SST-14 and SST-28, consist of 14 and 28 amino acids, respectively. In the endocrine pancreas SST secreted from δ-cells inhibits insulin and glucagon secretion [1]. SST acts via five somatostatin receptors (SSTR1–5), which belong to the G-protein coupled receptor (GPCR) family [2]. SSTR5 has a 10-fold higher affinity for SST-28 as compared to SST-14 [3]. It is believed that SST-28 via SSTR5 inhibits the release of insulin from β-cells, whereas SST-14 via the SSTR2 mediates the inhibition of glucagon release from α-cells [4,5]. In insulin secreting cells, SST inhibits glucose-induced electrical activity via activation of ATP-sensitive K^+-channels [6]. SST can also exert a direct inhibitory action on exocytosis of the insulin-containing granules [7].

In islets the subcellular localization of somatostatin receptors is under control of glucose and other insulin secretagogues [8]. Stimulation of islets with high glucose concentrations induces immediate recruitment of SSTRs from intracellular organelles to the plasma membrane. The SSTR translocation renders β-cells more sensitive to SST-induced inhibition of insulin secretion and, thus, can play an important role in paracrine regulation of insulin secretion by SST [9].

Intracellular trafficking as well as signalling by GPCRs are modulated by intracellular binding partners [10,11]. For SSTR5, we have recently shown that it binds to the PSD-95/discs large/zonula occludens 1 (PDZ) domain protein PIST (PDZ domain containing protein interacting specifically with Tc10) [12]. PIST is associated with the Golgi-apparatus and regulates the post-synthetic trafficking of the cystic fibrosis transmembrane regulator (CFTR) and other transmembrane proteins [13–15]. In HEK293 cells, the C-terminal PDZ ligand of the SSTR5 is required for post-endocytic sorting of the receptor from the Golgi-apparatus to the plasma membrane [14]. Here, we show that PIST is expressed in pancreatic β-cells, where it interacts with SSTR5. Interaction of these two proteins modulates SSTR5 receptor signaling and paracrine regulation of insulin secretion by SST.

2. Materials and methods

2.1. Islet isolation and MIN6 culture

Pancreatic islets were isolated from male Wistar rats (250–300 g, Charles River Laboratories, Sulzfeld, Germany) as described [16]. MIN6 cells were cultured in DMEM medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% (v/v) heat-inactivated fetal calf serum, 100 IU/ml penicillin and 100 μg/ml streptomycin (Invitrogen).

2.2. Fusion proteins and antibodies

Expression of glutathione *S*-transferase (GST) fusion proteins and purification using glutathione sepharose (AP Biotech, Freiburg, Germany) was performed as described by the manufacturer. The rabbit anti-PIST antibody, guinea-pig anti-PIST antibody [12] and rabbit anti-SSTR5 antibody [17] have been described before. Rabbit anti-insulin was obtained from Santa Cruz (H-86, Santa Cruz, CA, USA), Bip/GRP78, GM130 and annexin-II antibodies were obtained

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Abbreviations: CFTR, cystic fibrosis transmembrane regulator; EGFP, enhanced green fluorescent protein; GPCR, G-protein coupled receptor; GST, glutathione *S*-transferase; hGH, human growth hormone; PDZ, PSD-95/discs large/zonula occludens 1; PIST, protein interacting specifically with Tc10; SST, somatostatin; SSTR5, somatostatin receptor 5

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from BD Bioscience (Franklin Lakes, NJ, USA); and Lamp-2 and β COP antibodies were obtained from Affinity BioReagents (Golden, CO, USA).

2.3. Expression constructs

A fusion construct of the coding region of PIST with enhanced green fluorescent protein (EGFP) has been described before [12]. The coding region of the human growth hormone (hGH) was cloned into pCDNA3.1 (Invitrogen).

2.4. Pull-down assay

MIN6 cells were lyzed in RIPA-lysis buffer (50 μM Tris–HCl, pH 8.0, 150 mM NaCl, 1% NP-40, 0.5% Na-deoxycholate, 5 mM EDTA, 0.1% SDS, 0.2 mM phenylmethylsulfonyl fluoride, 1 μg/ml pepstatin, and 10 μg/ml leupeptin). Lysates were centrifuged (10 min; $10000 \times g$). GST fusion proteins were prepared and bound to glutathione beads (10 μg protein per individual experiment). The beads were incubated with cell lysate from the MIN6 cells for 2 h at 4 °C. Samples were precipitated by centrifugation and supernatants removed. After extensive washing of the beads with RIPA-lysis buffer, lysate and precipitate were analyzed by Western blotting using anti-PIST antibody.

2.5. Cell fractionation

MIN6 cells (equal cell numbers for each experiment) were lyzed in isotonic buffer (20 mM HEPES–HCl, pH 7.4, 1 mM $MgCl_2$, 1 mM EGTA, and 250 mM sucrose). Nuclei and cellular debris were removed by centrifugation ($1100 \times g$, 5 min, 4 °C). The supernatant was applied on top of a discontinuous sucrose gradient (0.6–2.0 M sucrose in 0.2 M steps in lysis buffer) and centrifuged ($100000 \times g$, 20 h, 4 °C). Fractions (8 μg protein) were characterized for subcellular organelle distribution as described previously [18].

2.6. Immunocytochemistry

MIN6 cells and dispersed islets cells were fixed with 4% paraformaldehyde in PBS. After blocking (5% normal goat serum, 2% BSA, 0.1% Triton X-100 in TBS) for 1 h at room temperature cells were incubated with guinea pig anti-PIST (1:1000) and anti-insulin (1:1000) for 2 h at room temperature, followed by Cy3- or Cy2-conjugated secondary antibodies (1:500). Immunostaining was visualized by confocal microscopy using a Zeiss LSM 410 microscope (Zeiss, Jena, Germany).

2.7. PIST protein expression

MIN6 cells were cultured for two days in DMEM medium containing 3 mM glucose with or without 1 μM SST-28. Cells were lyzed with RIPA-lysis buffer and PIST protein levels were analyzed by immunoblotting.

2.8. Insulin secretion measurement

MIN6 cells seeded in 96-well plates (30,000 cells per well) were cultured for three days. Cells were starved 1 h in Earle's Balanced Salt Solution (EBSS; Invitrogen) containing 1% BSA and no glucose. Measurements of insulin secretion were then performed in EBSS at indicated glucose concentrations and with substances of interest. Insulin in the supernatant was analyzed by ELISA.

2.9. Insulin and human growth hormone secretion and content measurement

MIN6 cells were co-transfected with expression vectors for EGFP-PIST (or EGFP alone) and human growth hormone (hGH) using the *The Nucleofector*™ Device (Amaxa GmbH, Köln, Germany). Transfected cells were seeded in 96-well plates (40,000 cells per well) and cultured for two days. Secretion measurements were performed as described above. Secreted hGH was detected in culture supernatants using the hGH ELISA (Roche, Mannheim, Germany). For measurement of the cellular hGH content, cells were lyzed (20 mM Tris–HCl, pH 7.4, 1% Triton X-100) before ELISA.

2.10. Statistical analysis

Results are presented as mean values ± S.E.M. for indicated number of experiments. Statistical significance was evaluated using Student's *t*-test for one-tailed unpaired data.

3. Results

MIN6 cells express PIST, as detected by a strong immunofluorescence signal. The bulk of the PIST-specific signal was co-localized with insulin. In addition, the insulin antibody (which does not differentiate between pro-insulin and insulin) labels some vesicular structures (presumably secretory granules) which do not contain PIST (arrows in Fig. 1). The co-localization of PIST and insulin is likely to occur in the Golgi-apparatus and is consistent with the previous observation of PIST localization in this cell-compartment [13]. This was confirmed by co-staining for the Golgi-specific marker, β COP. Also, in primary rat pancreatic β-cells, PIST was detected in all islet cells examined. In β-cells PIST was co-localized with insulin (Fig. 1).

The identity of the immunoreactive signal in MIN6 cells was further confirmed by Western blot analysis as well as by a pull-down experiment using a GST fusion protein of the SSTR5 C-terminus. We have previously shown that SSTR5 interacts with PIST via the C-terminal PDZ ligand motif [12]. The SSTR5 fusion protein (or GST control protein) was bound to a glutathione matrix and incubated with MIN6 cell lysate. PIST was detected in the lysate and was strongly enriched in the eluate from the SSTR5-GST matrix but not from the control GST matrix (Fig. 2A). Thus, PIST is present in MIN6 cells and can interact specifically with the C-terminus of SSTR5.

Subcellular fractionation by gradient centrifugation [18] revealed that PIST was abundant in a number of fractions of light and medium density, whereas SSTR5 was specifically confined to fraction 2, which was characterized as the plasma membrane-associated fraction (Fig. 2B). After treatment of cells with 1 μM SST-28 for 30 min, both PIST and SSTR5 relocated to the heaviest fraction (Fig. 2C), which displayed intensive staining with antibody against LAMP-2 (Fig. 2D), a lysosome marker. These data suggest that after treatment with SST-28, the SSTR5 is internalized and targeted into lysosomes, possibly due to its association with PIST.

We also examined whether activation of SSTR5 influences expression levels of PIST. Treatment of MIN6 cells with 1 μM SST-28 for 48 h reduced PIST expression levels by 55% when compared to control cells (Fig. 3).

SST inhibits insulin secretion via SSTR5 in pancreatic β-cells [4]. We examined the effects of SST-28, which preferentially activates SSTR5, on glucose-induced insulin secretion in MIN6 cells. Raising glucose concentration produced the expected increase in insulin secretion (Fig. 4A). SST-28 (5 and 50 nM) abolished this increase in insulin secretion, whereas basal insulin secretion was not affected by SST-28. In order to elucidate the role of PIST in SSTR5 signalling, we analyzed glucose-induced insulin secretion in MIN6 cells over-expressing PIST. Cells were transfected with a PIST-EGFP expression vector; overexpressed PIST-EGFP was localized in MIN6 cells in a pattern very similar to that of the endogenous PIST, i.e., co-localized with endogenous insulin (Fig. 4B). In order to evaluate hormone secretion only from cells, which were transfected with expression vectors, we co-transfected MIN6 cells with a vector coding for hGH. In this set-up, glucose-induced secretion of hGH was measured as a surrogate for insulin secretion [19]. No difference in basal hGH secretion was observed between EGFP and PIST-EGFP expressing MIN6 cells (Fig. 4C). However, cells expressing PIST-EGFP displayed a significant increase in glucose-induced hGH secretion as compared to glucose-

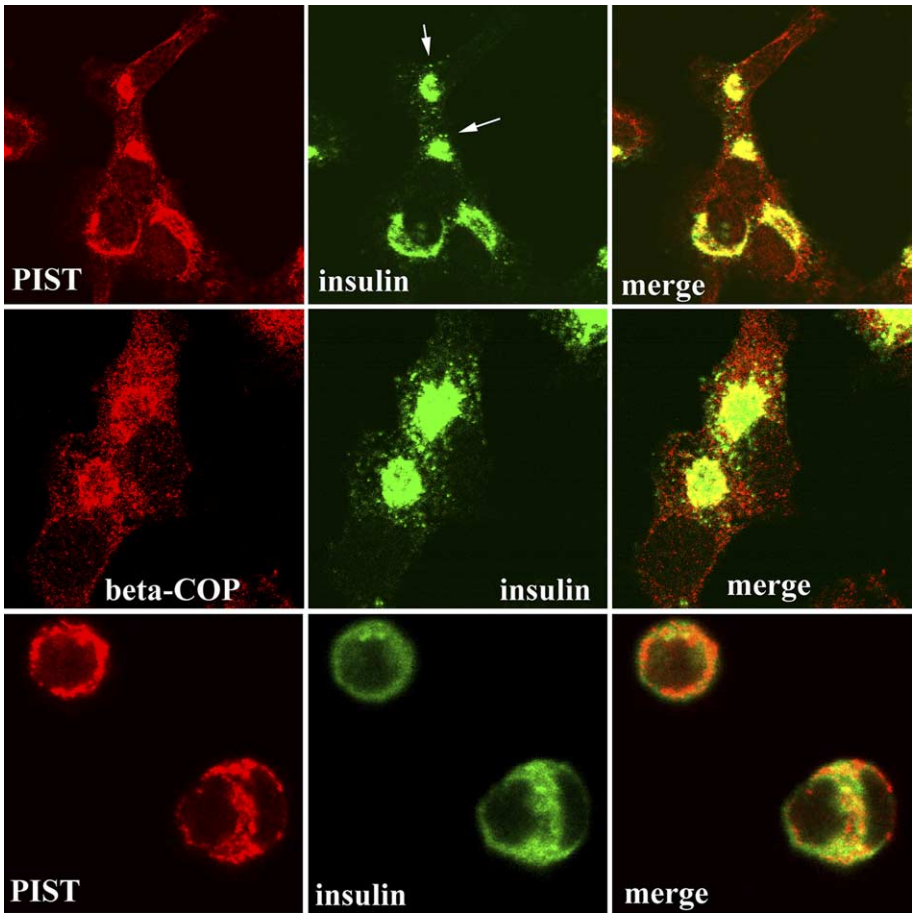

Fig. 1. MIN6 cells (upper, middle panels) or cells obtained by dispersing rat pancreatic islets (lower panel) were stained with anti-PIST, anti-β COP and anti-insulin antibodies as indicated. The merged pictures (right) display co-localization of insulin with PIST or βCOP, respectively. Arrows indicate vesicular labelling for insulin which is not coincident with PIST staining.

induced insulin secretion in cells transfected with the empty pEGFP control vector (Fig. 4C). In addition, SST-28 was found to be less potent in the inhibition of glucose-induced hGH secretion in cells expressing PIST-EGFP. Whereas 5 nM SST-28 completely inhibited the increase in hGH secretion induced with 20 mM glucose in mock transfected cells, the same concentration of the hormone produced only 50% inhibition of glucose-induced insulin secretion in cells over-expressing PIST (Fig. 4C).

The alleviation of SST-28 induced inhibition of hormone secretion by PIST overexpression suggests that PIST regulates insulin secretion by interfering with SSTR5 signalling. To further examine the role of SSTR5 in insulin secretion in MIN6 cells, we studied the effects of the specific SSTR5 antagonist BIM23056 [20]. Cells were treated with 1 μM BIM23056 for 1 h and insulin secretion was measured (Fig. 5). In cells treated with BIM23056, SST-28 does not inhibit insulin secretion indicating the efficiency of the antagonist in blocking signalling through SSTR5. Interestingly, cells treated with BIM23056 in the absence of SST-28 demonstrated an increase in glucose-induced insulin secretion similar to that in cells over-expressing PIST (Fig. 5). Taken together these data suggest that inhibition of SSTR5 activity can explain the increase in glucose-induced hormone secretion observed in MIN6 cells over-expressing PIST-EGFP.

4. Discussion

SSTR5 is known to inhibit glucose-induced insulin secretion in β-cells when activated by SST-28. SSTR5 deficient mice show increased basal and glucose-stimulated insulin secretion implying this receptor subtype in the paracrine regulation of insulin secretion by SST [5]. In islets, changes in plasma membrane SSTR concentration and receptor trafficking was suggested to be important for efficiency of paracine regulation of insulin secretion with SST [9]. Here, we show that PIST regulates SSTR5 signalling in β-cells.

We have shown previously that PIST interacts via its PDZ-domain with the C-terminal part of SSTR5 [12]. C-terminal interactions of SSTR5 are required to redirect the internalized SSTR5 back from the Golgi to the plasma membrane; in particular, overexpression of PIST retains the receptor within the Golgi-apparatus [12]. The role of PIST in the intracellular transport of transmembrane proteins extends to other proteins, such as frizzled [13], CFTR [14] and the β1-adrenergic receptor [15], all interacting with the PDZ-domain of PIST. PIST modulates intracellular trafficking via binding of its coiled-coil domain to the small GTPase Tc10 [21] and syntaxin-6 [22]. Syntaxin-6 is believed to function in the transport of post-Golgi vesicles to endosomes [23], whereas Tc10 is known for a role in the transport of secretory vesicles to the

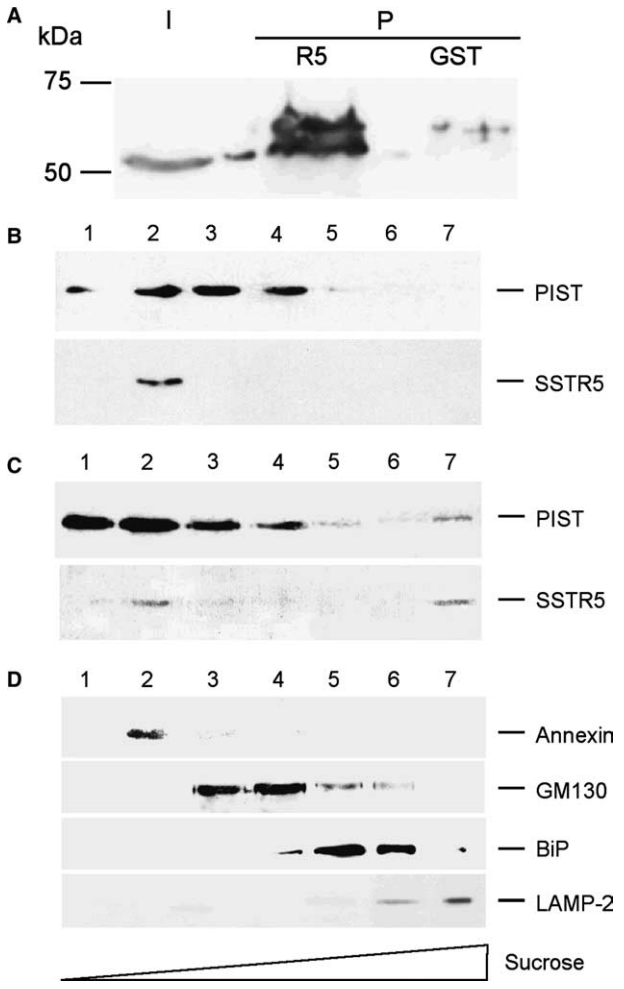

Fig. 2. Analysis of the interaction and subcellular distribution of PIST and SSTR5. (A) GST fusion protein of the C-terminus of rSSTR5 (R5) or GST alone (10 μg each) was incubated with glutathione beads and MIN6 cell lysate. Fractions of the initial (I) and the precipitated material (P) were analyzed by immunoblotting with anti-PIST antibody. PIST appears as a double band in precipitates, as described before [12], possibly due to aggregation. (B–D) MIN6 cells were treated without (B,D) or with 1 μM SST-28 (C) for 30 min. Cell homogenates were separated on a discontinous sucrose gradient (0.6–2.0 M sucrose). Fractions (8 μg protein content) were analyzed by Western Blotting using the antibodies indicated. Annexin is a marker for the plasma membrane GM130 for the Golgi, BiP (or GRP78) for the ER, and Lamp-2 for lysosomes.

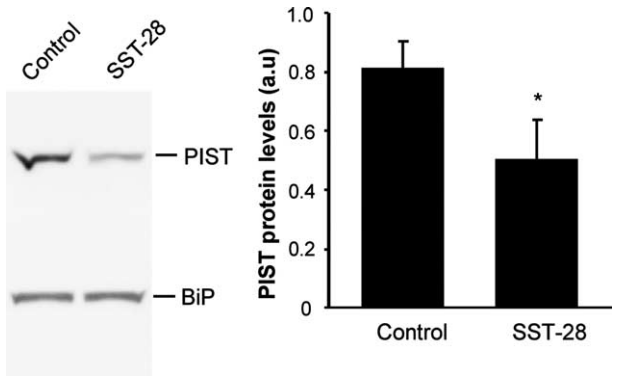

Fig. 3. Regulation of PIST protein levels by SST-28. MIN6 cells were cultured without (control) and with 1 μM SST-28 (SST) for 48 h. Expression of PIST and BiP (binding protein, also known as GRP78) in cell lysates was analyzed by immunoblotting (left panel). Protein expression was quantified (right panel). Data are means ± S.E.M. for three independent experiments. $^{*}P < 0.05$ versus PIST protein levels under control conditions.

plasma membrane [24]. Activation of Tc10 leads to increased transport of PIST and its associated CFTR from the Golgi to the plasma membrane, suggesting that the Tc10/PIST system provides a switch, which determines the distribution of specific membrane proteins between the plasma membrane and intracellular compartments.

Here, we show for the first time that PIST is expressed in pancreatic β-cells. We detected PIST in MIN6 cells as well as in rat islet cells. Subcellular fractionation shows that the SSTR5 is present at the plasma membrane, while PIST shows a wider distribution and is detected in the plasma membrane fraction as well as in the Golgi fractions. After activation of SSTR5 with its agonist SST-28, the receptor is internalized into a high-density intracellular compartment, which contains lysosomes (as well as secretory granules, data not shown). Interestingly, PIST follows SSTR5 and is also internalized into the same fraction. These data suggest that both proteins form an intracellular complex located most likely in endosomes/lysosomes, which is then subjected either to degradation or recycling back to the plasma membrane. Thus, in β-cells PIST can control trafficking of SSTR5 and thereby surface expression of the receptor.

The physiological relevance of the PIST–SSTR5 interaction was assessed by examining insulin secretion in MIN6 cells. As expected, insulin secretion in MIN6 cells was inhibited by low concentrations of SST-28. Interestingly, we observed by RT-PCR analysis that MIN6 cells express a relatively high amount of endogenous SST (data not shown). Similarly, SST expression has also been detected in a number of other insulinoma cell lines [25]. The SSTR5 specific antagonist BIM23056 enhances glucose-induced insulin secretion in the absence of exogenous somatostatin suggesting that insulin secretion in MIN6 is regulated in an autocrine manner by endogenous somatostatin.

Overexpression of PIST renders MIN6 cells more glucose-responsive and less sensitive to SST-28 inhibition. Inhibition of SSTR5 signalling with the receptor antagonist and overexpression of PIST produce the same functional effects. Considering that overexpression of PIST reduces the amount of SSTR5 present at the plasma membrane [13], our data suggest that MIN6 cells overexpressing PIST also display decreased SSTR5 levels located on the plasma membrane. Thus, the regulation of SSTR5 trafficking by PIST demonstrated previously in heterologous expression system contributes to the responsiveness of the native receptor in β-cells.

Interestingly, PIST protein expression in MIN6 cells is modulated by SST. We observed that PIST protein levels were downregulated after long-term treatment of cells with SST-28. Internalization of the receptors typically occurs for all SSTRs after prolonged treatment with agonists. One can speculate that under the conditions of decreased PIST level induced by agonist treatment, the internalized SSTR5 will be prevented from recycling back to the plasma membrane. SSTR5 may be targeted for degradation in the lysosomes instead. By this mechanism the cell would impose a constraint on chronic receptor activation.

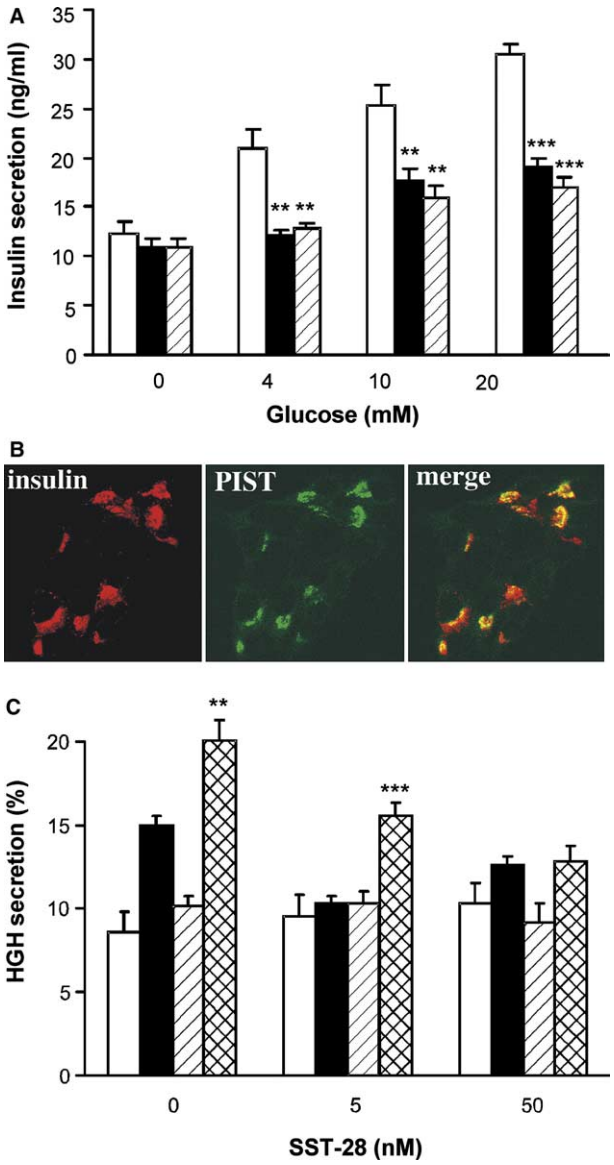

Fig. 4. Regulation of insulin secretion by SST-28 and PIST. (A) Insulin secretion was measured in MIN6 cells after incubation for 1 h at indicated glucose concentrations and 0 (white bars), 5 (black bars) or 50 (hatched bars) nM SST-28. Data are means ± S.E.M. for three independent experiments. $^{**}P < 0.01$ and $^{***}P < 0.001$ versus insulin secretion at the corresponding glucose concentration and no SST-28. (B) MIN6 cells were transfected with a PIST-EGFP. Insulin and PIST-EGFP were detected by staining with anti-insulin antibody (left) or the EGFP-autofluorescence (middle). (C) MIN6 cells were co-transfected with hGH/EGFP or hGH/PIST-EGFP. After treatment for 1 h with 0 or 20 mM glucose and different SST-28 concentrations hGH secretion was measured and normalized on hGH cellular content. EGFP transfection: 0 mM glucose, white bars; 20 mM glucose, black bars. PIST-EGFP transfection: 0 mM glucose, hatched bars; 20 mM glucose, crossed bars. Data are means ± S.E.M. for three independent experiments. $^{**}P < 0.01$ and $^{***}P < 0.001$ versus insulin secretion at corresponding glucose in cells co-transfected with hGH/EGFP.

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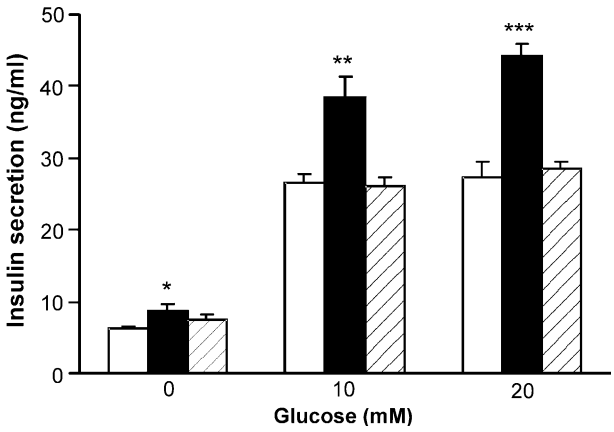

Fig. 5. Effect of SSTR5 antagonist on insulin secretion. Insulin secretion was measured in MIN6 cells treated for 1 h with 1 μM BIM23056 (black bars), 50 nM SST-28 and 1 μM BIM23056 (hatched bars) or without addition of peptides (white bars). Data are means ± S.E.M. for three independent experiments. $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ versus insulin secretion at corresponding glucose concentration and without peptides.

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